IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

REPLY BRIEF	ATTORNEY DOCKET NO. **70021.0022USU1**	
	U.S. APPLICATION SERIAL NO. **09/120,030**	CONFIRMATION NO **1743**
	FILING DATE **July 21, 1998**	
INVENTOR(S) **Beth P. GOLDSTEIN, et al.**	EXAMINER **Michael L. Borin**	GROUP ART UNIT **1631**
TITLE OF APPLICATION: METHOD FOR THE TREATMENT OF STAPHYLOCOCCAL DISEASE		

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ALEXANDRIA, VA 22313-1450

SIR:

This Reply Brief is submitted in response to the Examiner's Answer mailed on April 18, 2006.

I. STATUS OF CLAIMS

Claims 4, 5, 28, 32, 35, 44-51, 56-59 and 61-66 are currently pending. Claims 28 and 35 have been withdrawn.

II. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The issues presented for review are as follows:

(1) whether Claims 4, 5, 32, 44-51, 57 and 61-66 are patentable under 35 U.S.C. §103(a) over Zygmunt and Goldberg and Stark, and further in view of Oldham; and

(2) whether Claims 32, 46, 47, 50, 51, 56, 58 and 59 are patentable under 35 U.S.C. §103(a) over Zygmunt and Goldberg and Stark, and Oldham and further in view of Dixon.

III. ARGUMENT

Claims 4, 5, 32, 44-51, 57 and 61-66 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Zygmunt, Goldberg and Stark and further in view of Oldham. Claims 32, 46, 47, 50, 51, 56, 58 and 59 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Zygmunt, Goldberg, Stark and Oldham and further in view of Dixon. Each of these rejections is respectfully traversed.

The Examiner's Answer includes a discussion of each of the references applied against the claims (pages 3-9 of the Examiner's Answer). With respect to the Zygmunt reference, the Examiner's Answer states that the reference cites the use of " . . . multiple doses [of lysostaphin] in the range of 0.5 to 50 [mg/kg]" (page 4 of the Examiners Answer). The Examiner's Answer, however, is referring to the portion of the Zygmunt reference which discusses Goldberg (i.e., the bottom of page 323 of Zygmunt). As set forth below, however, the Goldberg reference does not provide motivation to administer 0.5 to 30 mg/kg/day or 0.5 to 25 mg/kg/day of lysostaphin to humans as set forth in the claims and, in fact, teaches away from the administration of such dosages to humans.

With respect to the Goldberg reference, the Examiner's Answer states that "[a]lthough lysostaphin administration was followed in relapse in some dogs (dogs 7 and 10), administration of lysostaphin caused from substantial reduction to complete clearance of infection. See Table 1." (page 4-5 of the Examiner's Answer). Table 1 of Goldberg, however, indicates that dogs 7 and 10 had significant levels of staphylococci in both blood and heart valve cultures. Moreover, according to Table 1 of Goldberg, dog 7 had 3,775 colonies/ml and dog 10 had 280 colonies/ml of staphylococci in blood cultures prior to autopsy. In contrast, dogs in the "well dogs" category had no more than 5 colonies/ml in blood cultures prior to autopsy. Similarly, in heart valve

cultures, dog 7 had 10^8 colonies/g in both aortic and mitral valve cultures whereas the dogs in the "well dogs" category had no more than 10^2 colonies/g in aortic valve cultures and no more than 10^3 colonies/g in mitral valve cultures. Moreover, according to Goldberg:

> [d]espite initial improvement, five dogs relapsed (relapsed dogs) 1.5 to 2.2 days after the first dose of lysostaphin. Although additional lysostaphin was administered after the relapse occurred in dogs 8 and 10, no effect on the course of the infection was apparent, and dog 10 subsequently expired. (page 48 of Goldberg)

The relapsed dogs are designated as Dogs 6-10 in Table 1 of Goldberg. Accordingly, Goldberg clearly discloses that the dogs in the "Relapsed Dogs" category, which includes Dogs 7 and 10, had a negative outcome. In fact, Dog 10 expired even though additional lysostaphin was administered after relapse occurred.

The Examiner's Answer also states that

> . . . the amount of lysostaphin which resulted in successful treatment of dogs (no relapse) of dogs 4 and 5 (Table 4), is only marginally different from the claimed amount of up to 30 mg/kg/day . . . as claimed in claims 4,5 or up to 25 mg/kg/day as claimed in claims 45-47." (page 5 of the Examiner's Answer)

This statement is unsupported by any evidence of record. As set forth in the MPEP, it is impermissible for the Examiner to base a rejection on a scientific proposition without providing ANY supporting evidence for that proposition. MPEP §2144.02. In addition, it is respectfully submitted that the differences between the dosage administered to Dog 5 in Goldberg and the claimed ranges are, in fact, significant. Moreover, the lowest dosage in mg/kg/day administered to a "well" or "improved" dog in Goldberg (i.e., 31.6 mg/kg/day administered to Dog 5) is more than 5 percent greater than the upper limit of the range recited in Claims 4 and 5. In addition, the dosage administered to Dog 5 is 26.4 percent greater than the upper range recited in Claims 45-47 (i.e., 25 mg/kg/day). Further, although the Examiner's Answer has acknowledged that there are differences between the claimed ranges and the dosages disclosed in Goldberg which resulted in the "successful treatment of dogs", the Examiner's Answer has pointed to no suggestion or

motivation in any reference to modify these dosages to arrive at the claimed invention.

In the discussion of the Stark reference, the Examiner's Answer states that Stark " . . . describes systemic administration of lysostaphin to a man suffering from staphylococcal pneumonia resulting from terminal unresponsive leukemia" (page 5 of the Examiner's Answer). The Examiner's Answer also states that Stark:

> demonstrates that parenteral systemic administration of lysostaphin reduces bacteremia caused by strain [sic] of *S. Aureus* which proved to be resistant to methicillin, vancomycin and cephalothin.

and that, according to Stark,

> [s]ingle treatment with lysostaphin resulted in a complete clearance of microorganisms from pustule sites . . . [and] removed staphylococci from blood, lungs, or abcess site (page 5 of the Examiner's Answer)

Stark, however, also discloses that "[s]ystemic use of lysostaphin in man has not been encouraged because of potential immunogenicity" and that " . . . its use in single, continuous, brief courses for overwhelming or unresponsive staphylococcal infections has been proposed" (page 239 of Stark). Stark then describes the administration of a *single* dose of lysostaphin to a human patient (page 240 of Stark). Stark therefore discloses that the systemic use of lysostaphin in humans may result in "potential immunogenicity" and is only recommended in "single, continuous, brief courses" (e.g., the dose administered to the patient in the study). Further, Stark discloses that an immune mediated anaphylactic response occurred after the systemic administration of just one dose of lysostaphin (page 240 of Stark). In contrast, Claims 4 and 5 recite systemically administering *multiple doses* of a lysostaphin analogue to a human. It is well established that a prior art reference must be considered in its entirety, i.e., as a whole including portions that would lead away from the claimed invention. MPEP §2141.02 VI. It is respectfully submitted that the disclosures in Stark that: 1) the systemic administration of anything other than

a "single, continuous, brief course" of lysostaphin to a human may result in "immunogenicity" and; 2) that even a single dose, when administered to a human, may have resulted in an immune mediated anaphylactic response; would lead one of ordinary skill in the art away from the claimed invention which involves the systemic administration of *multiple doses* of the lysostaphin analogue to a human.

In summing up the disclosures of Zygmunt, Goldberg and Stark, the Examiner's Answer states that "[i]n regard to the particular dosage ranges, first, Goldberg teaches dosage range [sic] that overlaps with the claimed dosage ranges" (page 6 of the Examiner's Answer). The dosages disclosed in Goldberg which are within the claimed ranges, however, resulted in relapse of the dogs being treated (i.e., Dogs 7 and 10). The Examiner's Answer also states that " . . if there are any differences between dosage ranges as claimed and that of the prior art, the differences would appear to be minor in nature; in addition as the dosage is an [sic] result effective variable, as can be clearly seen from, e.g., Goldberg, selection of the dosage, protocol and route of administration will be obvious to one skilled in the art as a result of routine optimization" (page 6 of the Official Action). As set forth above, however, the dosages disclosed in Goldberg which are within the claimed ranges resulted in relapse of the dogs being treated. In addition, the dosages which Goldberg indicated to be successful in dogs (i.e., the "well dogs" and "improved dogs") in all cases exceeded the dosage ranges recited in the claims. Accordingly, to the extent that Goldberg discloses that dosage is a "result effective variable", Goldberg suggests the use of dosages higher than those recited in the claims.

Additionally, it is respectfully submitted that the Examiner's Answer has failed to establish that the references could have been combined to arrive at the claimed invention with a reasonable expectation of success. In order to establish a *prima facie* case of obviousness, there

must be a reasonable expectation of success. MPEP §2143. Moreover, the prior art can be modified or combined to reject claims as *prima facie* obvious as long as there is a reasonable expectation of success. MPEP §2143.02. As set forth above, the dosages disclosed in Goldberg which are within the claimed ranges (i.e., the dosages administered to Dogs 7 and 10) resulted in relapse of the dogs being treated whereas the dosages which Goldberg indicated to be successful in dogs (i.e., the "well dogs" and "improved dogs") exceeded the dosage ranges recited in the claims. In addition, Stark discloses that the administration of anything other than a "single, continuous, brief course" of lysostaphin to a human may result in "immunogenicity". In fact, the patient being treated in Stark suffered an immune mediated anaphylaxis response with the systemic administration of just one dose. Accordingly, there would have been no reasonable expectation that the systemic administration of multiple doses of lysostaphin within the claimed dosage ranges would have been successful in treating staphylococcal infections in humans

Not only would a skilled artisan based on the teachings of these references not have been motivated to use lysostaphin systematically and in multiple doses, they would not have been motivated to co-administer the lysostaphin with another drug in view of the disclosure in Stark that the use of lysostaphin alone may have resulted in an anaphylactic response. Further, even assuming *arguendo* that one were motivated to use lysostaphin systematically, one would have been motivated to select a dosage higher than that claimed to avoid relapse (based on the disclosure in Goldberg) and a single dose so as to avoid toxicity problems (based on the disclosure in Stark). Interestingly, the Examiner has pointed to no other disclosures of the use of lysostaphin on humans which have been published since the publication of the Stark reference in 1974. This is consistent with the disclosure in Stark that one of ordinary skill in the art would not use lysostaphin except on a dying patient with a non responsive staph infection, and even then

would only administer a single dose at the site of the infection.

In the "Response to Argument" section of the Examiner's Answer, five different "reasons" are presented (there are two "reasons" denoted number "2"). Each of these "reasons" is addressed below.

In item "(1)", the Examiner's Answer relies upon the dosages administered to Dogs 4 and 5 of Goldberg which, as acknowledged in the Examiner's Answer, are outside of the claimed range. In particular, the Examiner's Answer states that there is only a "marginal difference" between dosages described as effective on dogs in Goldberg and the claimed ranges and that the claimed dosage is "in the same order" as that administered to Dogs 4 and 5 of Goldberg (page 9 of the Examiner's Answer). The Examiner's Answer then states that " . . it would be *prima facie* [sic] to an artisan that dosage demonstrated to be effective in dogs should be fine-tuned for use in humans" and that ". . . selection of the dosage would be obvious to one skilled in the art as a result of routine experimentation" (pages 9-10 of the Examiner's Answer). The Examiner's Answer is therefore apparently asserting that the disclosure of dosages outside of the claimed range in combination with a general suggestion to vary the dosage range in Goldberg provides motivation to administer dosages within the claimed ranges to humans. It is well established, however, that the mere fact that references can be modified does not render the resultant modification obvious *unless the prior art also suggests the desirability of the modification.* MPEP § 2143.01 III. It is also well established that a prior art reference must be considered in its entirety, i.e., as a whole including portions that would lead away from the claimed invention. MPEP §2141.02 VI. The reliance of the Examiner's Answer on dosages in Goldberg which were effective on dogs and outside of the claimed range (i.e., the dosages administered to Dogs 4 and 5) combined with the general teaching in Goldberg to modify the dosage does not establish *prima*

facie obviousness, particularly in view of the disclosure in Goldberg that the administration of dosages within the claimed range (i.e., to dogs 7 and 10) lead to relapse. Moreover, one of ordinary skill in the art would have had to proceed contrary to the teachings of Goldberg to arrive at the claimed invention. Thus, in order to arrive at the claimed invention, one of ordinary skill in the art would have had to employ dosages in humans which had been disclosed in Goldberg as resulting in eventual relapse and high levels of resistant strains in dogs. Accordingly, it is respectfully submitted that Appellants have, in fact, offered a "teaching to the contrary" (i.e., the teaching in Goldberg that the administration of dosages of lysostaphin within the ranges recited in the claims to dogs resulted in eventual relapse and to the development of high levels of resistant strains).

It is also respectfully submitted that, contrary to the unsupported assertions in the Examiner's Answer, the differences between the dosage administered to Dog 5 in Goldberg and the claimed dosage ranges are not "marginal" or "in the same order". As set forth above, the lowest dosage in mg/kg/day administered to a "well" or "improved" dog in Goldberg (i.e., 31.6 mg/kg/day administered to Dog 5) is more than 5 percent greater than the upper limit of the range recited in Claims 4 and 5. In addition, the dosage administered to Dog 5 is 26.4 percent greater than the upper range recited in Claims 45-47 (i.e., 25 mg/kg/day). Further, the Examiner has provided no scientific evidence that the dosages of 31.6 and 35.4 mg/kg/day disclosed in Goldberg are equivalent to the dosages recited in the claims.

In the first item "(2)", the Examiner's Answer relies on the dosages administered to Dogs 7 and 10. While acknowledging that these dosages resulted in relapse, the Examiner's Answer states that " . . . the instant claims are not excluding relapsing; rather, they are merely directed to 'treatment' of the infection" (page 10 of the Examiner's Answer). The Examiner's Answer also

states that " . . . for the dog 10 that received the smallest amount, 10 mg/kg/day, the amount of colonies/ml of blood dropped from 4,520 to just 16 in 2 hours. See Table 1." (page 10 of the Examiner's Answer). As set forth above, however, a prior art reference must be considered in its entirety, i.e., as a whole including portions that would lead away from the claimed invention. MPEP §2141.02(VI). Although Goldberg discloses the administration of dosages of lysostaphin within the ranges recited in the claims (i.e., from 0.5 to 30 and from 0.5 to 25 mg/kg/day) to Dogs 7 and 10, Goldberg also discloses that the administration of these dosages resulted in the eventual relapse of the dogs being treated. In addition, Goldberg discloses that dogs treated with these dosages had high levels of resistant strains (page 51 of Goldberg). Further, with respect to Dog 10, Goldberg discloses that "[a]lthough additional lysostaphin was administered after the relapse occurred . . . no effect on the course of the infection was apparent, and dog 10 subsequently expired" (page 48 of Goldberg). It is respectfully submitted that these disclosures in Goldberg would lead away from a method as claimed which involves administering from 0.5 to 30 or from 0.5 to 25 mg/kg/day of lysostaphin to humans.

It is respectfully submitted that one of ordinary skill in the art would not have been motivated to administer dosages of lysostaphin *to a human* in view of the disclosure in Goldberg that the administration of these dosages to dogs resulted in eventual relapse and the development of high levels of resistant strains in the dogs being treated. Further, even if one had been motivated to use lysostaphin to clear a staph infection, one would have chosen dosages higher than those recited in the claims based on the teachings in Goldberg.

In the second item "(2)" of the "Response to Argument" section, the Examiner's Answer states that "[i]t is well known that actual activity of antibiotics is batch dependent - this is why activity of antibiotics is often expressed in units of activity, rather than in absolute units like

mg/kg/day as in the instant claims" (page 10 of the Examiner's Answer). In order to support this assertion, the Examiner's Answer relies upon the Schuhardt reference (J. Bacteriol., Vol. 88, 1964, p. 815, lines 4-8) (See footnote 2, page 10 of the Examiner's Answer). Schuhardt, however, is a research study and not a clinical trial. In actuality, antibiotics are dosed based on drug weight to patient weight or drug weight per time unit and not by units of activity as stated in the Examiner's Answer. Furthermore, antibiotic activity is not batch dependent as stated in the Examiner's Answer. Manufacturing release criteria are pre-set and each batch of antibiotic must meet these criteria.

In item "(3)" of the "Response to Argument" section, the Examiner's Answer states that " [a]s the instant claims are drawn to recombinant lysostaphin, and Oldham demonstrated that recombinant lysostaphin has antimicrobial activity similar to the natural product, it would be obvious . . . that the dosage of recombinant lysostaphin . . . would have to be fine-tuned" (pages 10-11 of the Examiner's Answer). The Examiner's Answer, however, has failed to explain how the disclosures in the cited references can be "fine-tuned" to arrive at the claimed invention.

In item "(4)" of the "Response to Argument" section, the Examiner's Answer states that the " . . . instant specification itself supports the obviousness to determine a particular dosage range as it states that 'suitable dosages and regiments [sic] of lysostaphin may vary with the severity of infection and the sensitivity of the infecting organism' (see p. 10, lines 5-9)." It is well established, however, that the teaching or suggestion to make the claimed combination must be found in the prior art and not be based on applicant's disclosure. See MPEP §2142. Thus, it is improper for the Official Action to rely upon the applicant's disclosure to establish or "support" a *prima facie* case of obviousness.

The Examiner's Answer also states that, with regard to Goldberg, "there is no clear

indication in the reference that the lower the daily amount the more probable is development of resistant strains and eventual relapse of the dogs" (page 11 of the Examiner's Answer). Goldberg, however, contains the following disclosure:

> The highest proportions of resistant isolates after treatment were found in four of five relapsed dogs. Three of these dogs had received the smallest repeated doses of enzyme. When the largest single dose of enzyme was administered, as in dogs 3, 9, 11, and 12, resistant isolates were always in a minority. (page 51 of Goldberg)

As shown in Table 1, Dogs 3, 9, 11 and 12 each received a single dose of lysostaphin (page 48 of Goldberg). Goldberg therefore teaches that large single dosages result in a lower proportion of resistant isolates whereas smaller repeated dosages generally result in higher levels of resistant strains.

With regard to Stark, the Examiner's Answer states that the "reason the reference was used was to demonstrate that systemic administration of lysostaphin to a human is known in the art". As set forth above, however, a prior art reference must be considered *in its entirety*, i.e., as a whole including portions that would lead away from the claimed invention. MPEP §2141.02 VI. As also set forth above, Stark discloses that "systemic use in man has not been encouraged because of potential immunogenicity" and that "its use in single, continuous, brief courses for overwhelming or unresponsive staphylococcal infections has been proposed" (page 239 of Stark). In fact, the Examiner's Answer itself states that Stark "demonstrates that *just a single treatment* with lysostaphin resulted in a complete clearance of microorganisms from pustule sites" (emphasis added, page 12 of the Examiner's Answer). Therefore, to the extent Stark discloses systemic administration to humans, Stark discloses that lysostaphin should be administered in "single, continuous, brief courses". Claims 4 and 5, however, recite the systemic administration of *multiple* doses of lysostaphin and not a single dose.

With regard to Claims 44-51, the Examiner's Answer states that the " . . . Examiner does

not view 25 mg/kg/day as being substantially lower from, e.g., 31.6 mg/kg/day for dog 5 in the reference" (page 12 of the Examiner's Answer). To support this assertion, the Examiner's Answer then refers to the dosage range described in the specification. The Examiner's Answer, however, does not explain how the range recited in the specification relates to the difference between the dosage ranges recited in the claims and the dosage administered to Dog 5 in Goldberg. The Examiner's Answer also refers to the dosages administered to dogs 7 and 10 in Goldberg, which dosages are within the ranges recited in the claims. However, the administration of lysostaphin to each of these dogs was followed by relapse and resulted in the development of high levels of resistant strains. In fact, according to Goldberg, Dog 10 expired even though the administration of lysostaphin was resumed after relapse (page 48 of Goldberg). Thus, there is no support in Goldberg nor scientific evidence provided by the Examiner that lower doses of lysostaphin in the ranges recited in the claims, would clear infection. Rather, the contrary is suggested.

With regard to Claims 61-64, the Examiner's Answer states that "as to being 'cleared', this relative term does not mean complete removal and all the cited prior art teaches removal of, and thus clearance from, the infection" (page 13 of the Official Action). The term "clearance", however, precludes relapse. That is, if an infection relapses the infection has not been cleared even though the number of bacteria may have been reduced by the treatment to below detection limit levels since there is still a low level of infection that allows regrowth of bacteria. Accordingly, for the relapsed dogs in Goldberg (including Dogs 7 and 10) the infection could not have been "cleared" by the treatment. The Examiner's Answer also states that "[a]s for claims 62, 64, both Goldberg, on dogs, and Stark, on human, demonstrate a 'complete sterilization' achieved at least for some time and at least one site". The Examiner's Answer, however, has

pointed to no teaching in either reference of a method as claimed comprising administering 0.5 to 30 mg/kg/day to a human suffering from a staphylococcal infection wherein treatment results in complete sterilization of the infection.

In view of the foregoing and for the reasons set forth in the Appeal Brief filed on February 2, 2006, the rejections of all currently pending claims should be reversed.

Respectfully submitted,

MERCHANT & GOULD

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Date

Steven B. Kelber
Registration No. 30,073
Attorney of Record

Christopher W. Raimund
Registration No. 47,258

23552
PATENT TRADEMARK OFFICE

P.O. Box 2903
Minneapolis, Minnesota 55402-0903
Washington, DC 20005
Telephone: (202) 326-0300
Facsimile: (202) 326-0778